(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 555 042 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **93300737.9**

(22) Date of filing : **02.02.93**

(51) Int. Cl.[5] : **A61K 31/55,** A61K 31/44, G01F 11/24, G01F 11/46

(30) Priority : **06.02.92 JP 67901/92**

(43) Date of publication of application : **11.08.93 Bulletin 93/32**

(84) Designated Contracting States : **AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE**

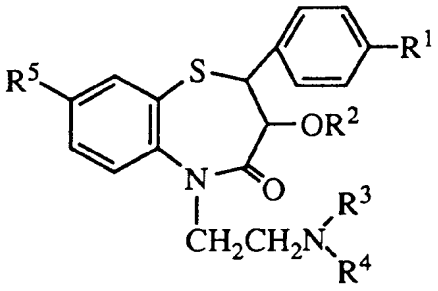
(71) Applicant : **TANABE SEIYAKU CO., LTD.**
2-10, Dosho-machi 3-chome
Chuo-ku Osaka (JP)

(72) Inventor : **Odawara, Akio**
205 City Chateau, No.15-15 Nishigaoka 1-chome
Kita-ku, Tokyo-to (JP)
Inventor : **Sasaki, Yasuhiko**
410 Urawa New Heights, No.85-1 Jinde
Urawa-shi, Saitama-ken (JP)
Inventor : **Murata, Sakae**
No.5-15, Kasumigaseki-kita 3-chome
Kawagoe-shi, Saitama-ken (JP)
Inventor : **Narita, Hiroshi**
No. 1436, Daimon
Urawa-shi, Saitama-ken (JP)

(74) Representative : **Hardisty, David Robert et al**
BOULT, WADE & TENNANT 27 Furnival Street
London EC4A IPQ (GB)

(54) Pharmaceutical composition for inhibiting platelet aggregation.

(57) There is disclosed a pharmaceutical composition for inhibiting platelet aggregation comprising 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and a 1,5-benzothiazepine derivative of the formula :



(I)

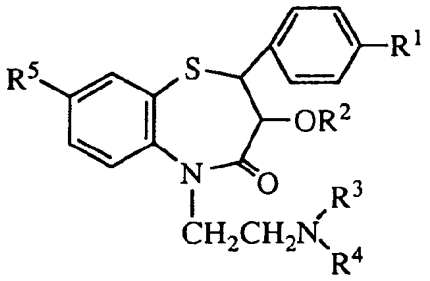
wherein R^1 is a lower alkyl group or a lower alkoxy group, R^2 is a lower alkanoyl group, R^3 and R^4 are a lower alkyl group and R^5 is hydrogen atom, a lower alkyl group or a halogen atom, or a pharmaceutically acceptable salt thereof.

EP 0 555 042 A1

This invention relates to a pharmaceutical composition for inhibiting platelet aggregation.

It is known that 1,5-benzothiazepine derivatives such as (+)-cis-2-(4-methoxyphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Diltiazem) and the corresponding 8-chloro-compound (Clentiazem) have an antihypertensive, coronary vasodilating and/or platelet aggregation-inhibiting activities (U.S. Pat. Nos. 3562257, 4567175 and 4590188). It is also known that 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Ticlopidine) is useful as the platelet aggregation inhibitor [(THE MERCK INDEX, TENTH EDITION, 1351 pages, 9272 (1983)].

As a result of the various investigations, the inventors of the present invention have now found that inhibitory effects on the platelet aggregation is enhanced in a synergistic manner by means of combined use of ticlopidine and the following 1,5-benzothiazepine derivatives, compared with either agent alone. Thus, according to the present invention, there is provided a pharmaceutical composition for inhibiting platelet aggregation which comprises ticlopidine or a pharmaceutically acceptable salt thereof and a 1,5-benzothiazepine derivative of the formula:



.(I)

wherein R^1 is a lower alkyl group or a lower alkoxy group, R^2 is a lower alkanoyl group, R^3 and R^4 are a lower alkyl group and R^5 is hydrogen atom, a lower alkyl group or a halogen atom, or a pharmaceutically acceptable salt thereof.

Example of the 1,5-benzothiazepine derivatives of the present invention may include the compounds of the formula (1), wherein R^1 is a lower alkyl group having 1 to 4 carbon atoms or a lower alkoxy group having 1 to 4 carbon atoms, R^2 is a lower alkanoyl group having 2 to 5 carbon atoms, R^3 and R^4 are a lower alkyl group having 1 to 4 carbon atoms and R^5 is hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms or a halogen atom such as chlorine, bromine and fluorine. Among them, preferred compounds (I) are those wherein R^1 is methyl or methoxy, R^2 is acetyl, R^3 and R^4 are methyl, and R^5 is hydrogen atom, methyl or chlorine.

Since the 1,5-benzothiazepine derivatives (I) of the present invention has two asymmetric carbon atoms at 2-position and 3-position of benzothiazepine ring, there exist two kinds of stereoisomers [namely, cis- and trans-isomers] and four kinds of optical isomers [namely, (+)-cis-, (-)-cis-, (+)-trans- and (-)-trans-isomers]. The present invention is inclusive of either of these isomers and their mixtures. Among them, preferred isomers are (-)-cis-isomer of the compounds of the formula (I) wherein R^1 is a lower alkyl group, R^2 is a lower alkanoyl group, R^3, R^4 and R^5 are a lower alkyl group, and (+)-cis-isomer of the compounds of the formula (I) wherein R^1 is a lower alkoxy group, R^2 is a lower alkanoyl group, R^3 and R^4 are a lower alkyl group and R^5 is hydrogen atom or a halogen atom.

The ticlopidine and 1,5-benzothiazepine derivatives (I) of the present invention can be used for medical use of either in free form or in the form of pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts of ticlopidine and compound (I) include, for example, inorganic acid addition salt such as hydrochloride, hydrobromide, sulfate and phosphate, and organic acid addition salt such as oxalate, acetate, maleate, fumarate, tartrate and methanesulfonate.

A preferred weight ratio of ticlopidine or a pharmaceutically acceptable salt thereof to the 1,5-benzothiazepine derivative (I) or a pharmaceutically acceptable salt thereof is 0.1 - 40 : 1, especially 0.3 - 10 : 1.

A preferred daily dose of ticlopidine or a pharmaceutically acceptable salt thereof is 20 to 200 mg, especially 30 to 100 mg, and that of the 1,5-benzothiazepine derivatives (I) or a pharmaceutically acceptable salt thereof is 5 to 200 mg, especially 10 to 100 mg, within the range of above-mentioned ratio.

Although the composition of the present invention can be used by way of either oral administration or parenteral administration, oral administration is preferred. In the case of oral administration, the composition of the present invention can be used as a pharmaceutical preparation together with a pharmaceutical carrier suitable for oral administration. The pharmaceutical carriers include, for example, conventional excipients, binders, disintegrators and lubricants (e.g., starch, lactose, glucose, gelatin, sorbitol, tragacanth gum, polyvinylpyrrolidone, sugar, corn starch, polyethylene glycol, talc, potassium phosphate and magnesium stearate). Further,

the dosage form may be a solid preparation such as tablets, pills, capsules and suppositories or it may also be a liquid preparation such as solutions, suspensions and emulsions. On the other hand, in the case of parenteral administration, the composition of the present invention may be preferably used as an injection, and as the pharmaceutical carrier for this purpose, for example, distilled water for injection, vegetable oil, propylene glycol, etc., can be suitably used. If required, a dissolving agent, a buffering agent and/or a stabilizing agent may be also employed.

As described above, the pharmaceutical composition of the present invention has excellent inhibitory effects on the platelet aggregation, and therefore it can be effectively used for treatment of coronary or cerebrovascular thrombosis, peripheral vascular disease, platelet aggregation disorders and migraine.

Furthermore, the pharmaceutical composition of the present invention shows a stronger platelet aggregation-inhibiting activity as compared with single use of each component and exerts an excellent synergistic effect. Namely, the dose of each component can be reduced by means of the combined use of the components in order to obtain an effect equivalent to that obtained by single use. Therefore, the pharmaceutical preparation of the present invention is high in safety and exerts a good effect.

EXPERIMENTAL EXAMPLE

Inhibitory effect on platelet aggregation

(Method)

Nine volumes of human blood were mixed with one volume of an aqueous 3.8 % trisodium citrate solution, and the mixture was centrifuged to give platelet-rich plasma (hereinafter referred to as " PRP") as the supernatant solution. The bottom layer was further centrifuged to give platelet-poor plasma (hereinafter referred to as " PPP ") as the supernatant solution. PRP was diluted with PPP so that the blood platelet counts were $4X10^5$ / mm^3. Then, 175 μl of said diluted PRP were added to a mixture of 25 μl of a solution of the following test compound (A), (B) or (C) and 25 μl of a solution of ticlopidine (D). After the mixture was stirred for 2 minutes at 37 °C, 25 μl of a collagen solution [Horm®, HORMON-CHEMIE] was added thereto, and the degree of platelet aggregation was measured by the method of Born [Nature, 194, page 927 (1962)].

In the control group, a mixture of 175 μl of diluted PRP, 25 μl of a solution of the test compound (A), (B), (C) or (D) and 25 μl of a physiological saline solution was tested.

Further, as a non-medicated control group, a mixture of 175 μl of said diluted PRP and 50 μl of a physiological saline solution was used.

Inhibitory effect on platelet aggregation is represented by the relative proportion of platelet aggregation of test compound(s) to that non-medicated control. It is calculated from the following formula.

$$\text{Inhibitory effect on platelet aggregation (\%)} = \frac{\text{Platelet aggregation (\%) of non-medicated control} - \text{Platelet aggregation (\%) of test compound(s)}}{\text{Platelet aggregation (\%) of non-medicated control}} \times 100$$

(Test compounds)

(A) (-)-cis-2-(4-methylphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-8-methyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one maleate (R^1, R^3, R^4 and R^5 = methyl, R^2 = acetyl.)

(B) (+)-cis-2-(4-methoxyphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-8-chloro-2,3-dihydro-1,5-benzothiazepin-4(5H)-one maleate (R^1= methoxy, R^2 = acetyl, R^3 and R^4 = methyl, R^5 = chlorine.)

(C) (+)-cis-2-(4-methoxyphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro- 1,5-benzothiazepin-4(5H)-one hydrochloride (R^1 = methoxy, R^2 = acetyl, R^3 and R^4 = methyl, R^5 = hydrogen atom.)

(D) Ticlopidine hydrochloride < i.e. 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride >

(Result)

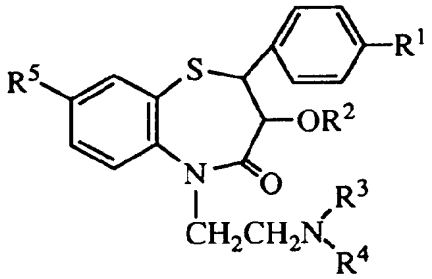
The results are shown in the following TABLE 1

TABLE 1.

	Concentration of test Compound (μg / ml)				Inhibitory effect on platelet aggregation (%)
	(A)	(B)	(C)	(D)	
The present invention	30	—	—	100	60.5
	—	30	—	100	60.5
	—	—	30	100	63.2
Control	30	—	—	—	21.1
	—	30	—	—	9.2
	—	—	30	—	11.8
	—	—	—	100	5.3

Claims

1. A pharmaceutical composition for inhibiting platelet aggregation, which comprises 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and a 1,5-benzothiazepine derivative of the formula:



(I)

wherein R^1 is a lower alkyl group or a lower alkoxy group, R^2 is a lower alkanoyl group, R^3 and R^4 are a lower alkyl group and R^5 is hydrogen atom, a lower alkyl group or a halogen atom, or a pharmaceutically acceptable salt thereof.

2. The composition according to claim 1, wherein R^1 is methyl group or methoxy group, R^2 is acetyl group, R^3 and R^4 are methyl group and R^5 is hydrogen atom, methyl group or chlorine atom.

3. The composition according to claim 1, wherein R^1 is methyl group, R^2 is acetyl group, R^3 and R^4 are methyl group and R^5 is methyl group.

4. The composition according to claim 1, wherein R^1 is methoxy group, R^2 is acetyl group, R^3 and R^4 are methyl group and R^5 is hydrogen atom or chlorine atom.

5. The composition according to claim 3, wherein said 1,5-benzothiazepine derivative is a (-)-cis-isomer.

6. The composition according to claim 4, wherein said 1,5-benzothiazepine derivative is a (+)-cis-isomer.

7. The composition according to any one of the preceding claims, wherein the weight ratio of 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof to the 1,5-benzothiazepine derivative (I) or a pharmaceutically acceptable salt thereof is 0.1 - 40 : 1.

8. The composition according to claim 7, wherein the weight ratio of 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof to the 1,5-benzothiazepine derivative (1) or a pharmaceutically acceptable salt thereof is 0.3-10:1.

9. A composition as claimed in any one of the preceding claims, wherein the composition comprises a pharmaceutical carrier and is suitable for oral or parenteral administration.

10. The use of a composition according to anyone of claims 1 to 8 in the preparation of a pharmaceutical formulation for the inhibition of platelet aggregation in the blood, said formulation being adapted to provide a daily dose of 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, of from 20 to 200 mg, and a daily dose of the 1,5-benzothiazepine derivative (I), or a pharmaceutically acceptable salt thereof, of from 5 to 200 mg.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 0737
Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	RECENTI PROGRESSI IN MEDICINA vol. 80, no. 1, 1989, pages 28 - 32 G. FINZI ET AL. 'Anticoagulanti orali ed antiaggreganti piastrinici nella prevenzione delle metastasi: stato dell'arte e prospettive di una terapia combinata' *page 31, last two paragraphs of conclusion* ---	1-9	A61K31/55 A61K31/44
Y	EP-A-0 255 141 (GÖDECKE AG) * claims 1-6 * ---	1-10	
Y	EP-A-0 214 881 (SYNTHELABO) * claims 1-2 * ---	1-10	
Y	US-A-4 080 447 (A. AMSELEM) * abstract; claims 1,4 * ---	1-10	
P,A	DIALOG INFORMATION SERVICES FILE NO. 72, EMBASE 1985-93 ACCESSION NO. 8612507 & VASA J. VASC. DIS. vol. 21, no. S34, 1992, pages 20 - 24 A.J. SMIT 'Medical treatment of peripheral vascular diseases: Are there new perspectives' * abstract * --- -/--	1-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	30 APRIL 1993	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 0737

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	DIALOG INFORMATION SERVICES FILE NO. 72, EMBASE 1985-93 ACCESSION NO. 7880871 & THER. SCHWEIZ vol. 6, no. 9, 1990, pages 680 - 681 A. THOMMEN 'Secondary prophylaxis of myocardial infarction' * abstract * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	30 APRIL 1993	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)